

# California M E D I C I N E

OFFICIAL JOURNAL OF THE CALIFORNIA MEDICAL ASSOCIATION

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Volume 89

OCTOBER 1958

Number 4

## Fungus Disease in Northern California

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LITTLE INFORMATION is available on the importance of fungi as a cause of disease in northern California. Coccidioidomycosis is a commonplace in the southern part of the Central Valley but other mycotic disease has not seemed to present a significant clinical problem. This study was designed to obtain information as to the incidence of infection with organisms of this group in the northern part of the state.

### PLAN OF STUDY

Materials were obtained from two sources. Information about the project was disseminated widely in the San Francisco Bay Area and assistance was offered gratis to all physicians and hospitals in the area. It was hoped that the mycologic laboratory of Stanford University School of Medicine would be employed as a reference center and that information would be obtained on fungus disease in other institutions. This phase of the program was successful in that 29 hospitals contributed materials from 185 patients in nearly all of whom systemic fungus infection was suspected. Also many specimens from patients with various forms of epidermophytosis were received from practicing physicians.

The most interesting aspect of the work centered around patients attending the clinics and admitted

• A systematic search for disease caused by fungi was made in a group of patients from northern California.

Superficial mycotic infection was diagnosed frequently. Systemic fungus infection was found in approximately 0.6 per cent of an unselected group observed at Stanford University clinics—coccidioidomycosis or actinomycosis in almost all cases.

Clinically unsuspected fungus infection was rare. Various species of *Candida* were frequently recovered, particularly from debilitated patients who had received antimicrobial therapy. Only rarely could these organisms be conclusively demonstrated to have caused serious disease.

to the wards of Stanford University Hospitals. Approximately 1,500 specimens were obtained from patients with possible superficial mycotic infection. The most important phase of the work consisted of mycological examination of unselected materials in certain categories that were submitted to the diagnostic bacteriological laboratory for study. Each was examined by the appropriate methods described below. A total of 1,254 patients was included in this group. It was believed that the application of this screening technique on a wide scale would detect unsuspected fungus infections if they were present in the community in significant number.

### METHODS

The following media were employed for the primary isolation of fungi from clinical materials.

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Supported by Grant No. E 786 from the National Institute of Allergy and Infectious Disease of the National Institutes of Health.

Submitted August 6, 1958.

**TABLE 1.—Species of Epidermophytes Grown on Cultures of Superficial Materials Obtained from 1,544 Patients**

Fungus	Number of Cases
<i>Microsporum audouinii</i> .....	214
<i>Microsporum canis</i> .....	57
<i>Microsporum gypsum</i> .....	4
<i>Trichophyton rubrum</i> .....	103
<i>Trichophyton mentagrophytes</i> .....	60
<i>Trichophyton tonsurans</i> .....	90
<i>Trichophyton violaceum</i> .....	1
<i>Epidermophyton floccosum</i> .....	13
Total .....	542

1. Saboraud Dextrose Agar (Difco) with and without antibiotics. The antibiotics used from the beginning of the study through November of 1956 were penicillin 1.0 units per ml., chloramphenicol 5.0 mcg. per ml., and streptomycin 10.0 mcg. per ml. After that date, the antibiotics used were chloramphenicol, polymyxin and neomycin, each in a concentration of 20.0 mcg. per ml. The latter combination was much more effective in the inhibition of growth of bacteria and did not affect the pathogenic fungi significantly.

2. Brain heart infusion agar (Difco).

3. Thioglycolate medium without dextrose (Difco).

The media were contained in appropriate screw cap bottles and tubes.

Materials obtained from superficial lesions were inoculated to Saboraud agar with antibiotics in duplicate and incubated at 22° C. Untreated materials from other sources were heavily inoculated to Saboraud agar with and without antibiotics in duplicate and incubated at 22° and 37° C. An anaerobic brain heart infusion agar plate and thioglycolate broth at 37° C. were also included.

The antibiotic-containing media were remarkably effective in inhibiting the growth of bacteria and had no effect on any of the species of fungi except actinomycetes and *Nocardia*.

## RESULTS

### Superficial Mycoses

The study of superficial mycoses was conducted in cooperation with the Division of Dermatology from July 1, 1953, through December 1, 1955. 418 specimens of hair, 974 of skin and 152 of finger and toe nails were examined. Potentially pathogenic fungi were recovered from more than one-third of these specimens. The species of epidermophytes recovered are listed in Table 1.

The large number of infections by *Trichophyton tonsurans* was of special interest. A description of some of these cases has been published.<sup>1</sup>

**TABLE 2.—Sources of Clinical Materials Used in Search for Systemic Fungus Infections**

Source	Number of Patients	Number Negative	Number Positive*
Sputum .....	548	372	166
Bronchial lavage, etc. ....	111	95	12
Gastric lavage, etc. ....	31	16	15
Pleural fluid .....	30	29	1
Abscesses, pus, wound drainage, sinus tract, cellulitis, etc. ....	134	114	17
Spinal fluid .....	37	37	0
Joint fluid .....	24	24	0
Blood .....	6	5	1
Biopsy of nodules, autopsies, cysts, tissue, etc. ....	149	143	4
Eye .....	17	16	1
Vaginal exudate .....	97	59	37
Nasopharyngeal .....	142	74	66
Urine .....	54	41	13
Stool .....	49	31	18
Cultures for identification .....	20	9	10
Total .....	1,449	1,087	361

\* Potentially pathogenic fungi.

**TABLE 3.—Fungi of Possible Significance Recovered from the Clinical Materials Listed in Table 2**

Organism	Number of Cases
<i>Candida albicans</i> .....	261
<i>Candida krusei</i> .....	12
<i>Candida parakrusei</i> .....	10
<i>Candida stellatoidea</i> .....	17
<i>Candida Guilliermondi</i> .....	3
<i>Candida tropicalis</i> .....	20
<i>Candida pseudotropicalis</i> .....	3
Total <i>Candida</i> .....	326
<i>Cryptococcus neoformans</i> .....	2
<i>Coccidioides immitis</i> .....	19
<i>Actinomyces bovis</i> .....	7
<i>Blastomyces brasiliensis</i> .....	1
<i>Nocardia asteroides</i> .....	5
<i>Nocardia madurae</i> .....	1
Total fungi other than <i>Candida</i> .....	35
Total all fungi .....	361

### Deep Mycotic Infection

The search for systemic fungus infections by the screening procedure described above continued from July 1, 1953, to August 31, 1957. Materials obtained from 1,449 patients including 1,254 in the Stanford University Hospitals group were studied. The sources of materials and the number from which a fungus of possible significance was isolated are listed in Table 2. The various species of fungi recovered are listed in Table 3.

More than 90 per cent of the organisms isolated were various species of *Candida*. The clinical significance of the presence of these fungi was usually difficult to assess. In many instances, when infection was present it was superficial. Of greater interest

was the identification of 19 cases of disease caused by *Coccidioides immitis*, seven by *Actinomyces bovis*, five by *Nocardia asteroides*, two by *Cryptococcus neoformans* and one each by *Blastomyces brasiliensis* and *Nocardia madurae*. A definite deep or systemic mycotic infection was present in 2.4 per cent of this whole group of patients.

**Pulmonary Infection.** Specimens of sputum and materials obtained by gastric and bronchial lavage were available from 690 patients. *Candida albicans* was isolated from 138 specimens and other species of this group of fungi from 44 specimens. It was difficult to determine whether these organisms which were often present in small numbers were the cause of disease. Twelve cases in which large numbers of *Candida* were repeatedly cultured from sputum were studied in some detail. In four of the patients, who were undergoing diagnostic study, no definite evidence of pulmonary disease was uncovered, two had lung abscess, one had far advanced cancer of the lung and one had extensive tuberculosis. Several of these patients had received antimicrobial therapy and it was evident that the presence of fungi was not related to the principal disease.

Large numbers of *Candida albicans* were recovered on several occasions from sputum specimens obtained from three elderly patients with senile emphysema and asthmatic bronchitis. All had had previous antimicrobial therapy, and they improved when such therapy was begun again in association with bronchodilator agents. In none of these cases could a diagnosis of fungus infection be established.

In the case of one debilitated, elderly man with disseminated carcinoma of the stomach, fever and rales in the chest developed. Large numbers of *Candida albicans* were present in the sputum, and no other significant organisms. The pulmonary infection resolved slowly after penicillin was administered, but it could have been pulmonary moniliasis.

The most interesting case was that of a 57-year-old man who had been well until two months before admission. At that time dyspnea began and became progressively more severe. The clinical impression was that of pulmonary fibrosis of unknown cause complicated by cor pulmonale. Laboratory study revealed eosinophilia of 20 per cent and a very high plasma content of gamma globulin. The presence of very large numbers of *Candida krusei* was noted in nine examinations of sputum, and the patient had exquisite hypersensitivity to the intradermal injection of a vaccine prepared from this organism. Treatment with an adrenal steroid and graded injections of the vaccine were associated with dramatic improvement for about three months. Then, in another community, all treatment was

discontinued and the patient failed rapidly and died. No autopsy was done. It seemed possible that in this case the illness was owing to infection by, and hypersensitivity to, *Candida krusei* with associated pulmonary fibrosis.

*Candida albicans* was twice recovered as one of a mixture of organisms from pleural fluid obtained from a patient with postoperative empyema and bronchopleural fistula complicating lobectomy. Recovery followed appropriate drainage of the pleural cavity.

*Coccidioides immitis* was cultured from material from ten patients, seven of whom were in outlying hospitals. Three strains were isolated from materials obtained from patients in the Stanford University Hospitals clinics, an incidence of 0.5 per cent of this group of unselected cases.

*Cryptococcus neoformans* was recovered from specimens of sputum obtained from two patients, one of whom was in another hospital.

One case of pulmonary nocardiosis and one of actinomycosis were recognized, both by study of specimens of sputum received from other hospitals.

These data demonstrate that fungus disease of the lungs may be discovered in northern California but is excessively uncommon when infection by *Coccidioides immitis* is excluded. The distribution and occurrence of this disease in the San Joaquin Valley has been studied in detail<sup>2</sup> and the infections discovered during this study were probably acquired in that area. No actinomycosis and only one case of *Cryptococcus* infection were discovered in the Stanford University Hospitals group of patients.

**Septic Infection.** Materials obtained from 134 patients with various apparently septic infectious processes were studied and significant fungi were recovered from 17 (12.7 per cent), only two of whom were members of the group studied in the Stanford clinics. Six of the infections were caused by *Coccidioides immitis*, six by *Actinomyces bovis*, three by *Nocardia asteroides*, one by *Nocardia madurae* and one by *Candida* sp. The last came from material obtained twice by incision and drainage of an abscess at a pressure point on the buttock under a prosthetic device worn by an amputee. In both specimens the organism was present in very large numbers. The abscess healed after the second operation.

**Body Fluids.** Spinal fluid obtained from 37 patients with various forms of central nervous system disease, and fluid from the joints of 24 persons with arthritis were studied and no fungi of any kind were isolated. *Candida albicans* grew on one of seven blood cultures examined. The infected specimen was from a man who died of postoperative sepsis. He had received tetracycline orally for two

weeks. *Staphylococcus aureus* also grew on the same blood culture.

**Tissue.** Specimens of tissues obtained at operation and necropsy from 149 persons in the Stanford clinic group were examined and *Coccidioides immitis* was obtained in three cases and *Candida krusei* in one. The latter case was one of acute leukemia in a child who died while under treatment with tetracycline for staphylococcic sepsis. At necropsy many small inflammatory nodules were observed in the lungs and spleen and large numbers of *Candida krusei* were isolated from the latter organ. Presumably the lesions were those of disseminated candidosis following treatment of a seriously ill patient with a broad spectrum antibiotic.

**Eye.** The organism *Nocardia asteroides* was isolated from material obtained from the tear duct of one patient.

**Gastrointestinal Tract.** Various species of *Candida* were recovered from 66 of 142 specimens obtained from nasopharyngeal swabs and from 18 of 49 specimens of stool examined. Many of these specimens that were positive for *Candida* were obtained from patients who had toxic gastrointestinal reactions to antimicrobial agents, particularly to the tetracycline. It was of interest to observe the absence of fungi in certain persons with these disorders and the inability to correlate their presence with the occurrence of symptoms in others receiving antibiotics.

**Genito-urinary Tract.** *Candida albicans* was recovered from 36 and *Candida parakrusei* from one of 97 specimens of vaginal exudate that were examined. Many of the patients doubtless had vaginitis but detailed analysis of this group was not attempted.

Various species of *Candida* were found in the urine of 13 of 54 patients with urinary tract infection. The organisms were present in large numbers in six cases and these deserve comment. In five cases the patients had structural disease of the urinary tract; they had received antimicrobial therapy and had undergone catheterization or instrumentation of the urinary tract. The fungi did not seem to cause signs or symptoms of an unusual sort and were present in pure culture in only three cases. The sixth case was of greater interest. A six-week-old boy was treated with neomycin by mouth for diarrhea, caused by an enteropathogenic *E. coli*, that developed while he was in hospital for study of a congenital lesion of the heart associated with cardiac decompensation. Shortly thereafter he became febrile with pneumonitis and pyuria. Large numbers of *Candida albicans* were recovered from the urine. A urethral catheter had not been used. Death occurred within two weeks in another hospi-

tal and necropsy was not done. This was a case of probably disseminated Candidosis with pneumonitis and pyelonephritis following therapy with a broad spectrum antibiotic by mouth in a very sick baby.

#### Identification

Potential pathogens grew on ten of twenty cultures of fungi submitted purely for identification. Seven were various species of *Candida*, two were *Nocardia asteroides*, and one was *Coccidioides immitis*.

#### DISCUSSION

This study was designed to assess the frequency of infection and the importance of fungi as a cause of disease in northern California. The results indicate that superficial mycotic infections were a commonplace but systemic illness caused by these organisms was uncommon.

Approximately 2.5 per cent of the whole group of patients studied were infected by *Coccidioides immitis*, *Nocardia asteroides*, *Actinomyces bovis*, or *Cryptococcus neoformans*. A considerable number of the subjects studied were in other hospitals and were a selected group in whom fungus disease was known or suspected to be present.

Materials were obtained from the lungs and related structures, and from other organs and tissues of 1,254 patients in a group observed at Stanford University Hospitals and Clinics in San Francisco. Most of these examinations were made routinely without reference to whether the patient was thought to have a mycotic disease or not. Infection by these four kinds of fungus was proved in eight (0.6 per cent) of the patients in the whole group in which disease caused by these organisms was considered possible. The incidence would have been greater if the source of the materials had been more carefully screened. In several of the eight cases the clinical situation suggested mycotic disease. It is evident that the routine examination of a very large number of clinical specimens does not uncover many instances of unsuspected systemic fungus infection.

*Candida* in large numbers were recovered from the sputum, from material obtained on nasopharyngeal swabs and vaginal swabs and from stools of a considerable number of patients, many of whom had received antimicrobial therapy. It was nearly always difficult to assess the role of these fungi in the causation of various manifestations of the patient's illness. In no case was pulmonary Candidosis definitely diagnosed and in only three was there positive evidence of disseminated infection caused by these organisms. One case of localized abscess formation containing *Candida* sp. was observed.

Mycotic infection must always be considered in persons with possible infectious diseases, particularly of the lungs. The results of this study indicate that the search for this group of organisms in northern California will not often be rewarding except for the demonstration of coccidioidomycosis.

Candida of various species are often recovered from clinical materials but the role they play in the causation of disease is always difficult to ascertain. Serious infection by this group of organisms is

most likely to occur in debilitated persons who have received antimicrobial therapy.

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#### REFERENCES

1. Joseph, H. L., and Halde, C.: Tinea capitis due to Trichophyton tonsurans, Calif. Med., 83:371, 1955.
2. Smith, C. E.: Coccidioidomycosis. The Pediatrics Clinics of North America, Feb., 1955. Vol. 2, No. 1. W. B. Saunders and Co., pages 109-125.

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